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Review Article

COVID-19 vaccination in pregnancy: A review of maternal and infant benefits

Emmanuel Lamptey^{a,c,*}, Ephraim Kumi Senkyire^b, Moses Tia Banoya^c, Stanley Yaidoo^d^a Institute of Life and Earth Sciences (Including Health and Agriculture), Pan African University, University of Ibadan, Nigeria^b Ga-West Municipal Hospital Ghana Health Service, Ghana^c Methodist University, Ghana^d St. Gregory Catholic Hospital Kasoa, Ghana

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ABSTRACT

Pregnant women with COVID-19 are more likely to be admitted to the intensive care unit and their babies born prematurely. Clinical trials excluded pregnant women from the vaccine and safety data were limited. However, an increasing number of studies have demonstrated the safety and immunogenicity of the COVID-19 vaccines for pregnant women and their babies including evidence of maternal transfer of antibodies. In addition to these benefits, the vaccines are proved to be effective for both the pregnant women and infants. The current evidence supports the safety, immunogenicity of the COVID-19 vaccine and its effectiveness in reducing the theoretical risk of the infection among pregnant women and their infants. This review summarizes the recent data on the beneficial effects of COVID-19 immunization on both the pregnant mother and infant.

1. Introduction

Pregnant women are more susceptible to COVID-19 infection and severe illness due to physiological and immunological changes.^{1,2} The infection spreads quickly through the maternal vasculature, and the symptoms manifest after an incubation period of one day to 14 days with a mean of 4.5–5.8 days.^{3,4} Inflammatory cytokines (IL-1, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor, interferon- α -inducible protein 10) and tumour necrosis factor α are seen to increase in the blood, placental and vagina samples of pregnant women following COVID-19.^{5,6} The high levels of these mediators, together with fall in T cells and rising leukocytes and neutrophils-lymphocyte ratio have been associated with the severity of the infection and its related complications.^{1,7,8}

Seroprevalence studies suggest that women in both the first, second and third trimester of pregnancy have an equal risk of contracting the virus, but severe complications are higher in the third trimester.^{9,10} There are high rates of admission to ICU for women who test positive for the infection with the potential to develop pre-eclampsia and the need for

an emergency caesarean at the time of birth.¹¹ Women of black, Asian and minority descent and those aged 35 years with a BMI of 25 or more having the underlying condition of hypertension and diabetes are more vulnerable to these complications.¹² A study done on September 25, 2020, by the U.S Centre for Disease Control and Prevention among 598 pregnant women with confirmed cases reported more hospitalization and ICU admission of expectant mothers than non-pregnant women.¹³ The present review evaluates the extent of immunogenicity, safety and clinical outcomes of the vaccine to the mother and their babies. This paper summarizes relevant studies and data assessing these benefits of the COVID-19 vaccine in pregnant women and their newborns.

1.1. Effect of COVID-19 on pregnancy

Pregnant women across the globe have faced many uncertainties since the arrival of the SARS-COV-2.¹⁴ For instance, the hypercoagulability of pregnancy makes women susceptible to blood clot formation. Patients with COVID-19 show increased risk of clotting suggesting that

* Corresponding author. Institute of Life and Earth Sciences (Including Health and Agriculture), Pan African University, University of Ibadan, Nigeria.

E-mail address: emmanuelamp88@gmail.com (E. Lamptey).

pregnant women have more potential risk of maternal venous thrombosis.¹⁵ This may be worsened by reduced mobility due to hospital admission.¹⁵ The implications do not only affect the pregnant mother but also the fetus and the neonate as well.¹⁶

There is emerging evidence that vertical transmission is possible but occur in minimal cases of infected pregnant women.^{17,18} In one retrospective cross-sectional study of 45 newborns from mothers with COVID-19, 3(6.6%) tested positive by throat swab.¹⁹ In a related event, out of 836 babies born to infected women, 35 of them (4.2%) were confirmed positive by a polymerase chain reaction, and they showed no respiratory complications.²⁰ Walker et al. reported that 8/292 newborns from infected expectant women tested positive on vaginal delivery while 20/375 were caesarean section.²¹ IgM antibodies for SARS-CoV-2 are identified in neonatal serum at birth.^{22,23} These reports imply neonatal immune response to the virus in-utero because it is well known that IgM antibodies do not cross the placenta. Neonates born to COVID-19 mothers, although showed no SARS-CoV-2 infection, exhibit perinatal complications with placental tissues confirmed positive for the virus.²⁴ A review done by Yang et al. reported the following adverse fetal and neonatal outcomes: preterm birth (21.3%); stillbirth (1.2%); fetal distress (10.7%); neonatal deaths (1.2%), and neonatal asphyxia (1.2%).²⁵ In a study by Chan et al. spontaneous and induced abortion was reported among 6% of pregnant women with the COVID-19 infection.²⁶ Similarly, a single center study in China also reported 5.3% cases of neonatal distress in babies born to COVID-19 women.²⁷ Other studies have also reported premature rupture of membrane and fetal distress in a review.²⁸ Placental inflammation during SARS-CoV-2 infection may result in fetal growth retardation and induced abortion.²⁹ Newborns of women with the infection have significantly higher severe neonatal morbidity index, perinatal morbidity, and mortality index.³⁰ Inflammatory responses from maternal SARS-CoV-2 infection affect the brain development of the fetus that could predispose them to mental illness in the future.³¹ Even though there is limited and unclear data about COVID-19 in pregnancy, some studies have contrasting views. It is established that high fevers in pregnancy raise the risk of birth defects.¹² The impact of the COVID-19 virus on both the mother and the infant implies that pregnant women should be proactive when it comes to vaccination.¹²

The burden on pregnant women and their infants have led to the increasing interest in antenatal immunization campaigns to protect mothers and their young ones. The CDC, the American College of Obstetricians and Gynecology (ACOG), the society for maternal and fetal medicine (SMFM) support the recommendation of COVID-19 vaccination in pregnancy to all pregnant, lactating individuals along with those planning to get pregnant.¹²

1.2. Safety concern of COVID-19 vaccination

While COVID-19 infection escalates the risk of severe illness and death in pregnant women, pregnant women were not integrated in the primary vaccine trials.³² Consequently, safety information is scarce. Countries have different recommendations, yet they have approved the COVID-19 immunization in pregnancy after a risk-benefit analysis.³² However, the Joint Committee on Vaccination and Immunization (JCVI) of the United Kingdom lately endorsed an mRNA vaccination for pregnant women. Immunization is also commended by the CDC, ACOG, ARFM, and WHO. Not long ago, India with the ICMR and the Ministry of Health and Family Welfare advocate vaccination during pregnancy and lactation.³²

According to Developmental and Reproductive Toxicity (DART) experiments of the Pfizer-BioNTech COVID-19 vaccine in Europe, there were no complication on pregnancy, embryo/fetal development, parturition, or post-natal development in animals given the vaccination.³³ The same study involving Moderna's mRNA-1273 in rats by given a dose of 100 µg before copulating and during gestation cycles had no adverse effects on female reproduction, fetal/embryonal development, or post-natal developmental outcomes, except for skeletal variations, which are

common and typically resolve postnatal without intervention.³³

Moreover, 1 mL of Janssen COVID-19 vaccine was also administer to female rabbits proved no vaccine-associated harmful effects on female fertility, embryo-fetal development, or postnatal development.³³ Initial animal trials for Covishield revealed no adverse effects on fertility, pregnancy, embryo-fetal development, parturition, or postnatal development.³⁴ For Covaxin vaccine, its safety in pregnancy is to be determined.³⁵ Conversely, the ministry of health in India has endorsed both Covishield and Covaxin for vaccinating pregnant and lactating women and has been judged safe.³⁶

Wolf et al. found production antiplatelet antibodies after exposure to the "AstraZeneca COVID-19 vaccination," resulting in thrombocytopenia and venous thrombotic events.³⁷ These events, which range from deep vein thrombosis to pulmonary embolism, splanchnic, portal or hepatic vein thrombosis, CVST, and ocular vein thrombosis, befell 5–21 days after COVID-19 vaccine delivery in unanticipated places such as the abdomen and brain.³⁸ However, in a study in the USA of 46 079 pregnancies revealed that immunization against covid-19 was safe and did not increase the risk of preterm birth or small for gestational age babies.³⁹ This was in consonance with observational studies from the USA, Norway and Israel which found no risks related to mRNA COVID-19 vaccines administered during pregnancy.⁴⁰ Again, population-based observational retrospective studies from Sweden, Norway and Canada assessing results in more than 250 000 pregnancies provided strong evidence concerning safety of COVID-19 vaccination in pregnancy.⁴¹ These studies found no associated increased risks for postpartum hemorrhage, chorioamnionitis, cesarean delivery, neonatal care admission, or low Apgar score. All these findings are extremely in consistent with previous evidence globally. Despite previous validated trials, there are ongoing trials pending data safety. A prospective observational study is being conducted by Janssen which aim to quantify obstetric, neonatal, and infant outcomes. Objectively, Janssen will oversee a phase 2 placebo-controlled trial in more than 800 pregnant women.⁴² Considering the paucity of data, the known risk of coronavirus disease during pregnancy is likely to outweigh the not yet fully elucidated risk of SARS-CoV-2 vaccines reassuring safety and efficacy. To assess the safety, tolerability, and immunogenicity of the SARS-CoV-2 vaccination in pregnant women aged 18 and older, Pfizer will start its randomized placebo-controlled observer blind global second phase trial including 4000 vaccinated pregnant women between 24 and 34 weeks.⁴² To determine whether to receive the vaccine or the placebo, each woman will take part in the study for 7–10 months, and their neonates will be observed till they are 6 months old.⁴²

1.3. Benefits of COVID-19 vaccination during pregnancy for pregnant women

Studies have evaluated the immunogenicity, safety and tolerability of some of the COVID-19 vaccines in pregnant women.⁴³ More reliable and reassuring information derived from the Vaccine Adverse Event Reporting system justifies maternal immunization and suggest that the COVID-19 vaccine be administered to pregnant women.⁴³

Collier et al. analyzed the immunogenicity of the mRNA vaccine in 22 pregnant women and 6 non-pregnant unvaccinated women with SARS-CoV-2 infection. The receipt of the vaccine was immunogenic in pregnant women, and vaccine-elicited antibodies were transported to infant cord, blood and breast milk.⁴⁴ In a related cohort study, Gray et al. found that COVID-19 messenger RNA vaccination in pregnancy and lactation generate robust humoral immunity similar to that observed in non-pregnant women. Vaccination allows the immune system of expectant mothers to be trained to recognize the spike protein of the SARS-CoV-2 infection.⁴⁵ Also, the side effects profile of pregnant women who receive the COVID-19 vaccine is not significantly different from the non-pregnant population.⁴⁵ With mRNA vaccines, comparable humoral immunogenic responses are developed in both pregnant, lactating and non-pregnant populations.⁴⁵ Data available indicate that

pregnant/breastfeeding women can generate a satisfactory immune response after COVID-19 vaccination. In a study that took serum samples of pregnant, non-pregnant 21 days after second vaccine dose and 26 days for lactating mothers after receiving mRNA-1272 and BNT162b vaccines respectively.⁴⁶ Sufficient antibody titre against COVID-19 and the new variant is generated with pregnant/lactating women.⁴⁶ T-cells responses were presented in both pregnant and non-pregnant women to the variant of concern suggesting cellular immune response is strong.⁴⁶

In addition to these immunogenicities, Shimabukuro TT et al. reported preliminary findings of mRNA covid-19 vaccine safety in pregnant persons from three U.S vaccine safety monitoring systems: the “v-safe after vaccination health checker”, the V-safe pregnancy registry and the vaccine adverse events reporting system (VAERS).⁴⁷ The study included data from these three sources from December 12, 2020, to February 28, 2021, and participants were aged 16–54 years.³⁴ Among 2211 pregnancy-related adverse events reported to the VAERS, 46/221 were spontaneous abortions. For the V-safe pregnancy registry, 827 participants had a completed pregnancy, 115 recorded losses and 712 (86.1%) were live births.⁴⁷ The calculated proportion of adverse outcomes were similar to incidences in the pre-pandemic period. Early data from these sources did not find any safety concerns for pregnant women and their babies.⁴⁸ These preliminary findings did not show any signal or caution among pregnant women who received the mRNA COVID-19 vaccine.⁴⁷ Except for intrapartum fever or temperature measuring above 38 reported by less than 1% of the participants on day 1 after the first dose and by 8% of the second dose, there were no intrapartum complications.^{47,49} Still in the U. S, a prospective cohort study conducted among adults who are pregnant, lactating or planning pregnancy at the time of vaccination (Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273) indicated that the odds of severe reactions were statistically decreased among individuals who were pregnant.⁵⁰

The COVID-19 vaccines and the experiences among this group are well tolerated when compared with non-pregnant women.⁵⁰ In another prospective observational cohort study in which vaccinated and non-vaccinated pregnant women were recruited. The rate of composite pregnancy complications was similar between the vaccinated and the non-vaccinated group (15.8% vs 20.1% $p = 0.37$), and the risk of COVID-19 was lower in the vaccinated group (1.5% vs 6.5%, odds ratio:4.5, $p = 0.024$).⁵¹ mRNA COVID-19 vaccines during pregnancy do not seem to increase the rate of pregnancy complications and are effective in the prevention of the infection.⁵¹ These findings contribute to the mounting evidence that, COVID-19 vaccination in pregnancy is safe and the vaccine do not alter perinatal outcomes or cause maternal death.^{49,52}

The efficacy of the COVID-19 vaccines in pregnant women is demonstrated in several observational studies. A retrospective study in Israel proved that the Pfizer-BioNTech vaccine (BNT16b2) messenger RNA is 78% effective at preventing asymptomatic and symptomatic SARS-COV-2 infection in pregnant women.⁵³ Seven thousand five hundred and thirty pregnant (7530) vaccinated women were matched by age, gestational age, the number of times they had given birth, flu vaccination status and population sub-group with their unvaccinated counterpart. The study represented 27% of the Israeli population recruited in a large state-mandated healthcare organization.⁵³ The incidence of SARS-COV-2 in the unvaccinated group was almost twice in the vaccinated population (202/118).⁴⁰ However, outcomes of symptomatic infection were almost the same in both groups (83.8% vaccinated group vs 83.2% unvaccinated group).⁵³ Another study among pregnant and lactating women found the vaccine helpful in developing cross-reactive antibody and T-cell responses against the SARS-COV-2 variant of concern.⁴⁴

These two factors are the main reasons the vaccines should be given due consideration by pregnant women and their care providers. Hence there is no concern for the high incidence of fever or potential risk to the fetus. In a nutshell, the risk of administering COVID-19 vaccines during pregnancy appear to be minimal. It outweighs any theoretical and remote risk of vaccination, and there is a long term solution against a future wave of COVID-19.⁵⁴

Patients with conditions such as diabetes, obesity, and preeclampsia still stand the chance to benefit from immunization against SARS-COV-2. The likelihood of poor maternal and neonatal outcome which increases with SARS-COV-2 infection become preventable with vaccination.⁵⁵ It plays a vital role in the prevention of COVID-19 morbidity in pregnant patients. These are direct and compelling evidence of maternal benefits of COVID-19 vaccination in pregnancy, irrespective that clinical trials did not verify the safety of the vaccine.

1.4. Infant protection associated with COVID-19 immunization

Neonates can acquire SARS-COV-2 in-utero from mothers with COVID-19 because of elevated IgM antibodies to SARS-COV-2 detected in neonates.^{56,57} One in 4 of all babies born to women with COVID-19 need admission to the neonatal unit or specialist care.⁵⁸ Although the effect of SARS-COV2 on infants and neonates appear to be small or not well known. The infection has led to a significant risk of preterm births, fetal distress, respiratory distress, thrombocytopenia, and severe neonatal/perinatal morbidity index.^{56,59} This burden warrants the recommendation of antenatal immunization to protect both the mother and the infant.

An immunogenicity study conducted by New York University Langone Health showed high levels of antibodies passed to babies. Antibodies crossing the placenta is a good thing and good safety data.⁶⁰ The study which aimed to determine the maternal, neonatal and obstetric outcomes of 424 pregnant women who received a messenger RNA COVID-19 vaccine (Pfizer BioNTech) while pregnant found that cord blood from mothers had high anti-S IgG level because of maternal immunization.⁶⁰ Thus, the effectiveness of the vaccine triggered the production of the antibodies capable of protecting the newborn from the infection.⁶⁰ Their work also looked at antibodies to the nucleocapsid protein (anti-N1gG) which were not seen suggesting the vaccine trigger antibodies to spike protein but not the prior infection. The significant vertical transfer of antibodies came from maternal vaccination rather than natural infection.⁶⁰ Robust and comparable IgG titers are stronger in vaccinated pregnant women than the unvaccinated ones who got COVID-19.⁴⁵

Antibodies also make their way to provide passive immunization via the milk of a lactating mother. The IgG antibodies are specific to vaccine response while IgA which comes from breastmilk following natural infection and recovery from COVID-19 and is present in all vaccine types.^{61,62} In women already breastfeeding, the robust antibodies (IgG and IgA) are generated 6 weeks following vaccination with the Pfizer-BioNTech.⁶³ These generated antibodies may protect the baby in the first several months of life when the child is most vulnerable.⁶⁴ The breastmilk also contains a large amount of IgA and IgG against SARS-COV-2 after the second dose of the COVID-19 vaccine.⁶³ Amid the beneficial antibodies, studies are suggesting that there is an optimal trimester for the mother to get the jabs for maximum benefits. COVID-19 shots earlier in pregnancy are suggested to be better for the baby.⁶⁵ The sooner pregnant women can get the vaccine the more likely the transfer of high level of protective antibodies.⁶⁵

A study that analyzed the blood and umbilical cord of 27 expectant women who received Pfizer Moderna vaccines pointed that a longer period between vaccination and delivery guarantees effective transfer of COVID-19 antibodies (immunoglobulin G) to newborns.⁶⁶ Antibodies (IgG) were not seen in the blood sample of women who took the jabs less than 3 weeks before delivery.⁶⁶ With factors associated with the efficiency of transfer, second dose vaccination significantly increased infant IgG levels. Infant antibody levels were also equal to maternal levels.⁶⁶ There is no increased risk during pregnancy in the form of birth complications to the mother or the fetus among those who received the vaccine. In one study, the rate of spontaneous abortion and preterm birth recorded 6.5% and 5.9% respectively which were within or below the figures of the pre-pandemic period or national average.^{60,67} In a similar event reported in the UK, the number of miscarriages and stillbirths

registered in the summary of yellow for the COVID-19 vaccine was low to the number of pregnant women who received the COVID-19 vaccines.⁶⁸

In summary, these studies show that COVID-19 vaccination in pregnancy help to develop enough antibodies to protect the infant and mother from the infection. This show that the COVID-19 vaccines are able to prevent severe infection in two lives at once (mother and baby). In addition, difficulty in caring for the newborn due to severe illness from the infection can be prevented which is an incredible way for pregnant women to use their body and breast milk to protect their newborns.⁶⁹ There is also the chance that the infant may come into contact with other family members or caregivers who may not be vaccinated where infection prevention is a concern. Joint statement of strong medical consensus from the leading organizations representing experts in maternal care support vaccination of pregnant individuals against SARS-CoV-2.⁷⁰

2. Conclusion

This review shows that COVID-19 vaccines in pregnancy are safe, effective and beneficial. Pregnant individuals are more likely to get severely ill with COVID-19, and their newborns have a higher risk of being born prematurely. The vaccine protects pregnant women, and newborns also benefit from COVID-19 vaccinated mothers. Several studies have proved these benefits of the vaccine on both the mother and the baby. These findings support the vaccination as the best way to protect pregnant women and their babies against the known risk of SARS-CoV-2. With the increasing severity of COVID-19 in pregnancy amid the delta variant surge,⁷¹ pregnant women should be prioritized for COVID-19 vaccination while those planning conception need not delay taking the vaccines.

Conflict of interest

No conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gocm.2022.07.003>.

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